THE GLYKOGENIC FUNCTION OF THE LIVER.

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BY JAMES TYSON, M. D., PROFESSOR OF PHYSIOLOGY AND MICROSCOPIC ANATOMY.

It has been customary to arrange the *phenomena* of *healthy life*, the consideration of which is the object of the science of Physiology, into two grand divisions, the functions or phenomena of *organic* life, and those of *animal* life, or the functions of relation. The former are common to all animals and vegetables, being those by which simple vegetative existence is maintained; while the latter, or animal functions, are peculiar and confined to animals, being the phenomena by which all but the lowest forms are distinguished from vegetables.

The *organic* functions include *Generation*, or the function by which the individual is reproduced, and the species preserved; *Digestion*, or the process of the preparation of food; *Absorption* and *Sanguification*, by which the prepared aliment is introduced into the vessels, and converted into blood; *Circulation*, the function by which the blood is distributed throughout the economy; *Respiration*, through which the blood is ærated or acted upon by oxygen, and relieved of its carbonic acid; *Nutrition*, a still imperfectly understood process in which new material is laid down in the place of the old, which, in turn, is taken up and carried to the sewers of the body; *Secretion*, a process allied to nutrition, in which certain fluids and solids are separated from the blood, either to be used again as milk, or to be thrown out as useless or harmful, as the ingredients of urine; and finally *Calorification*, through which the uniform heat of the individual is maintained.

The *Animal Functions* or functions of relation are *Sensation*, *Voluntary motion*, *Mental and Moral Manifestations*. *Moral* manifestations are peculiar to man, constituting the cardinal characteristic by which he is distinguished from the so-called brute creation, to which must be permitted *mental* manifestations, at least in their general significance. But through his moral manifestations, man is enabled to conceive the Good, the True, and the Beautiful, and to comprehend also, the existence of a Supreme Being. These are conceptions of a highest intelligence, and by these man signalises himself rather than by a more perfect physical organization.

In all systematic treatises on Physiology, it is customary to take up these several functions, and consider them in detail; and such, indeed, will be the general method in this course of lectures. But so vast has become the amount of material at the disposal of the physiologist, that it would be

quite impossible to state even all well-determined facts in the limited time allotted to lectures in the American system of medical education. So that a deviation from a strict observance of such a plan has become necessary in recent times, as the result of which it is found best to omit any effort at including all known facts of physiological science, but to confine ourselves to the demonstration of crucial matters; while it is attempted, also, to indicate to students the paths by which they can at once complete their information upon known points, and at the same time extend the boundaries of a science, the most fertile in unexplored treasures. To do this, we must seek a practical familiarity with the means which contribute most to this end.

The agents which have added most largely to our knowledge of physiological science are the *microscope* and *experiment*. The use of the former has been sufficiently illustrated in the preliminary lectures which I have given you in the past five weeks. I will not, therefore, occupy your time with any further consideration of it. But some of the results of the latter, I propose to illustrate in the course of the present hour. For this purpose I have selected the *glykogenic* or sugar-forming function of the liver, which I hope to be able to demonstrate to your satisfaction.

In 1848, Claude Bernard, while seeking for the place in the body where the sugar derived from alimentary substances disappears, discovered sugar in the blood of the hepatic veins of dogs which had been fed for seven days exclusively on meat, and confirmed his results by repeated experiments. Thence he concluded, that sugar was formed in the liver, and was contained in the blood coming from that organ, independently of the diet of the animal. He also made extracts of the organ itself, and found it always contained sugar, while the other tissues of the economy were entirely devoid of it. Subsequently, he found it in the livers of nearly all animals, including man.

That sugar is not only present, but produced for some time after death in the dead liver is easily demonstrated. I have upon this plate a portion of dog's liver removed two days ago. It is therefore preëminently dead liver. Taking a part and rinsing it in cold water I cut it into smaller pieces, conveniently with a pair of sharp scissors, allowing the fragments to fall into this capsule of boiling water, to which an excess of crystallized sulphate of soda is added. After allowing the mixture to boil for two or three minutes the whole is poured into a mortar, compressed with the pestle, and then thrown upon an ordinary filter. The object of the sulphate of soda is to clarify the extract. The same thing is accomplished, though with more time and trouble, by filtering through animal charcoal. The filtrate is then a clarified aqueous extract of liver which is supposed

to contain sugar. On cooling, abundant crystals of sulphate of soda deposit upon the sides and bottom of the vessel, but these do not interfere with the test. To determine the presence of sugar, I add, to a portion of this solution in a test-tube, a few drops of Fehling's* solution, a modified Trommer's test, and apply heat. Almost immediately after the boiling process begins, you note the reduction of the oxide of copper and the precipitation of the red suboxide.

This liver, then, undoubtedly contains sugar. Nor is this alone true. If a stream of water is passed through the portal vein, it will wash out the sugar there present, and if a piece of the organ be thus extracted and tested in the way I have shown you, it would not respond to the copper test. But if it be allowed to remain a few hours at rest, and then again tested, sugar will be found present, showing not only the presence of sugar in the liver, but that it is *produced* in this organ after death.

To prove, however, that the liver is a sugar-forming organ during life, something further is necessary; and Bernard further established the two following propositions, which I will also attempt to demonstrate: first, that no sugar is found in the blood of the portal vein of animals fed upon nitrogenous or non-saccharine and non-amylaceous articles; second, that sugar is found in the blood of the hepatic vein of these same animals.

In this test-tube I have an extract of the blood from the portal vein of the dog whose liver I have just tested, and which I prepared in a similar manner. Let us apply the Fehling's test. You note that the boiling point is attained, and that the process is continued for several minutes, and yet no reduction takes place. There is, therefore, no sugar in this extract of the portal blood. In the second tube, I have an aqueous extract of the blood taken from the hepatic vein of the dog whose portal blood we have just tested. I apply the same test, and you note the reduction which takes place of the protoxide of copper. Not nearly so

*The following are the proportions to be used in making Fehling's Solution, taken from p. 147 of Dr. Roberts' "Urinary and Renal Diseases:"

40 grammes crystals of sulphate of copper,
160 " neutral tartrate of potash.
750 " caustic soda, sp. gr. 1.12.

Add water up to 1154.5 cub. centimetres.

Ten cub. c. correspond to 0.05 gramme of grape sugar.

It is well known that Fehling's Solution is liable to change on standing, so that if boiled, a precipitate takes place, even though no sugar is present. To obviate this risk, Dr. Flint prefers to make three separate solutions, which are to be mixed just before using, as follows —(Flint, Physiology of Man, Vol. III, p. 301:)

Solution of crystallized sulphate of copper, 90½ grs. in a fluid ounce distilled water.

Solution neutral tartrate potash, 364 grs. in a fluid ounce distilled water.

Solution caustic soda, specific gravity 1.12.

Take half a fluid drachm of the copper solution, add half a fluid drachm of the solution of tartrate of potash, and add enough solution of caustic soda to make three fluid drachms. Two hundred grains of this solution accurately made are exactly decomposed by one grain of sugar.

marked, it is true, as when applied to the extract of the dead liver, but sufficiently so to satisfy us of the presence of sugar in this situation,—that is, in the blood coming from the liver.

Thus would appear to have been demonstrated the sugar-forming function of the liver. But the faith of many physiologists was for a time shaken by the results of the experiments of Schiff, Meissner, and Jaeger, of Germany, and especially of Pavy, of London, whose experiments were repeated with like results by M'Donnell, of Dublin. These experimenters declared that the liver did not actually contain sugar during life, but that the production of sugar was post mortem; that the liver produced, during life, the sugar-forming substance called by Bernard *glykogen* or *zoamyline*, but that the transformation of this substance into sugar did not take place in the living state, but after death.

These objections seemed at first well founded, for it can readily be shown that the living liver does not contain sugar. The dog which I now introduce has had nothing to eat for several hours. I propose removing in your presence, a piece of the liver, which shall be as nearly as possible in the condition of the living organ, and without the administration of an anæsthetic, the use of which is attended by the appearance of sugar in the general circulation. The usual plan is to break up the medulla oblongata, but I propose here to administer prussic acid. A few drops of the strong acid are placed upon the animal's tongue, and in a few seconds, though not actually dead, he is beyond all suffering. Opening the abdomen and thorax quickly, the heart is seen to be still beating, the lungs expanding and collapsing. A piece of liver is rapidly cut out, rinsed in cold water, cut into small pieces in the capsule of boiling water, and treated as was the piece of the dead organ. The test liquid is applied, and you notice there is no response. The living liver therefore contains no sugar. What then is the state of the case? Does this prove that the liver is not a sugar-forming organ? Physiologists are, without doubt, indebted to Prof. Austin Flint, Jr., of New York, for the solution.

In September, 1869, Dr. Flint published a paper entitled "Experiments undertaken to reconcile some Discordant Observations upon the Glykogenic Function of the Liver," as the result of which he concluded that sugar is constantly formed in the liver but is discharged into or washed out by the blood of the hepatic veins. In an experiment performed before the class of the Bellevue Hospital Medical College by Prof. Flint, January 4th, 1869, upon a medium sized dog in full digestion of meat, the medulla oblongata was broken up; the portal vein was tied through a small opening in the abdomen, the abdomen then widely opened, a portion of the liver excised, rapidly rinsed and cut up in boiling water—the length of time between the breaking up of the medulla and cutting up the liver being

one minute. The vena cava was then tied above the renal veins, the chest opened, and the cava again tied above the hepatic vein. Blood was then taken from the hepatic veins, an equal bulk of water added, with an excess of crystallized sulphate of soda, and the mixture boiled. A portion of the portal blood and the decoction of the liver were then treated in the same way, and the three specimens filtered. The clear extracts were then tested with Fehling's liquid, with the following result: There was no sugar in the portal blood, none in the extract of the liver. There was a *marked reaction in the extract of the blood from the hepatic veins*, the precipitate rendering the whole solution bright yellow and entirely opaque.

Our experiments to-day have sufficiently confirmed these results, and though they would seem amply conclusive, Dr. Pavy replied to Dr. Flint, "that so quickly is sugar formed in the liver after death that the result was to have been expected, considering the expenditure of time involved in applying the ligatures." This objection can, of course, only refer to the presence of sugar in the hepatic vein, since the results of Dr. Flint's experiments, as well as the one performed before you to-day, coincide with those of Pavy as to the absence of sugar in the living organ.

We believe the question to have been definitely settled by the recent experiments of Prof. W. T. Lusk, of New York City, whose paper "On the Origin of Diabetes" is contained in the New York Medical Journal, for July, 1870. Dr. Lusk's experiments consisted *first*, in the removal of blood by catheterization from the right side of the heart, and from the jugular vein; *second*, in testing with a carefully diluted Fehling's solution the alcoholic extracts of these bloods. The results clearly showed that the quantity of sugar in the right side of the heart was two to four times greater than that found under corresponding circumstances in the jugular vein, and from this he justly concluded that there was by no means an insignificant amount of sugar in the pure hepatic blood, before it has become largely diluted with the comparatively non-saccharine fluids of the venæ cavæ, and thence that the liver "is certainly, under normal conditions, the principal source of sugar in the economy."

These observations, then, would lead us to accept the conclusions of Prof. Flint, Jr., as apparently confirmed by the demonstrations of this lecture, but especially by the crucial experiments of Dr. Lusk. Our own conclusions are, then, those of Prof. Flint, which we accordingly append from p. 315 of his third volume, that including "Secretion, Nutrition, Movements."

1. "A substance exists in the healthy liver which is capable of being converted into sugar; and inasmuch as this is formed into sugar during

life, the sugar being washed away by the blood passing through the liver, it is perfectly proper to call it glykogenic or sugar-forming matter.

2. "The liver has a glykogenic function, which consists in the constant formation of sugar out of the glykogenic matter, this being carried away by the blood of the hepatic veins, which always contain sugar in a certain proportion. This takes place in the carnivora as well as in those animals that take sugar and starch as food; and it is essentially independent of the kind of food taken.

3. "During life the liver contains only the glykogenic matter and no sugar, because the great mass of blood which is constantly passing through this organ washes out the sugar as fast as it is formed; but after death, or when the circulation is interfered with, the transformation of glykogenic matter into sugar goes on; the sugar can then be detected in the substance of the liver."

It should also be stated, that the animal from whose portal and hepatic blood were made the extracts used in this lecture, was placed under the influence of an anæsthetic, the objection to the use of which has been alluded to. But since the comparison was made between the portal blood going *to* the liver, (which alone could obtain sugar, on the supposition that nitrogenous food only is used, from the systemic blood through the cœliac axis and superior mesenteric artery,) and between the same blood passing *from* the liver, and since the former was found *not* to contain sugar, we do not think any valid objection can be made to the use of ether. In analyses of blood obtained from the cavities of the heart, the omission of the anæsthetic is more essential.